## REMARKS

The undersigned thanks Examiner Wilder for the helpful telephonic interview on June 9th, summarized herein. Amendments are submitted herewith as discussed during the interview.

**Rejection under 35 U.S.C. § 103(a)**

Claims 1-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lander, et al. (WO 98/20165, May 1998) in view of Buck, et al. (Biotechniques, vol. 27, no. 3, pages 528-536, 1999) and further in view of Hiratsuka, et al. (Clinical Biochemistry, vol. 35, pages 35-40, 2002).

As correctly stated in the Office Action, Lander, et al. teach neither the nucleic acid probe ending in nucleotide number 196 of SEQ ID NO: 2 nor labeling of the 3' terminal cytosine with a fluorescent dye which decreases upon hybridization. However, the Office Action takes the position that the claimed probes are structural homologs of the oligonucleotides taught by Lander, et al.

In order to clearly distinguish the claimed invention from the cited references, claim 1 has been amended to closed language so that the probes of Lander, et al. are clearly not included in the claimed subject matter. Furthermore, there is no teaching in Lander, et al. on a fluorescent label specifically at the cytosine at position 196 as claimed.

The position of the label is not taught by any of the cited references and is critical to the claimed invention. Among the many cytosines that could be labeled for detection of β3 adrenaline receptor mutations, the cytosine at 196 of SEQ ID NO: 2 is critical for detecting the Trp64Arg mutation by Tm analysis. Furthermore, the Trp64Arg mutation is not taught by any of the cited references. As there is no recognition in the cited references of a mutation of residue 64, there is no apparent reason to make a probe falling within the scope of claim 1. Even if the Trp64Arg mutation is known, there is no teaching on the criticality of labeling at position 196 for detection of the mutation.

When probes as claimed are used, which have cytosine at the 3' end (position 196), changes in fluorescence intensity that could be analyzed by Tm analysis were observed (see specification, page 12, first 5 lines of text). Labeling of the cytosine at position 196 with a fluorescent label, which is not taught by Lander, et al. or any of the cited references, is critical to detection of the Trp64Arg mutation by Tm analysis.

Buck, et al. is cited to show that the substitution of the oligonucleotide of Applicant for the oligonucleotide of Lander, et al. is an obvious substitution of equivalents for the same purpose.

First, Buck, et al. is directed to sequencing primers, not probes for Tm analysis. Accordingly the purpose of Buck, et al. is different than the purpose of Applicant. To the extent that Buck, et al. support the position that one sequencing primer may be substituted for another, one cannot extrapolate that because sequencing primers are equivalent, that probes for Tm analysis will also be equivalent.

Importantly, the data in the specification (see page 12, first 5 lines of text) rebuts the Examiner's arguments based upon Buck, et al. that probes for Tm analysis will be equivalent. Clearly, from the specification, not all probes are equivalent because only 5 of the probes tested were able to function in Tm analysis.

Hiratsuka, et al. teach Tm analysis to determine a mutation in a nucleotide sequence in a nucleic acid encoding a beta2-adrenergic receptor. However, Hiratsuka, et al. do not teach the probe claimed by Applicants and do not teach the mutation at position 64. There was no apparent reason to prepare the probes as claimed at the time of the claimed invention because there is no recognition in the cited references of a mutation at position 64.

Furthermore, method claims 3-6 have been amended to add an active method step of hybridizing the probe (as specified in claim 1) "with a nucleic acid having a single nucleotide polymorphism site at position 64 in the amino acid sequence of the β3-adrenergic receptor" and that the method performed using the probe as claimed allows for detection "of copy number as low as 20 genomic copies". Support for the amendment is found in the present specification at page 3, lines 29-31, at page 5, lines 16-27, and page 12, last full paragraph.

None of the cited references teach detection of a polymorphism at position 64 of the β3-adrenergic receptor. None of the cited references teaches detection of as few as 20 genomic copies. None of the cited references teach the specific probes of 7-30 nucleotides of SEQ ID NO: 2 labeled at position 196 as claimed.

In view of Applicant's amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

**No Disclaimers or Disavowals**

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

**CONCLUSION**

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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